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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/480,236	01/10/00	DIGAN M	4-31157A/USN

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EXAMINER	
EWOLDT,G	
ART UNIT	**PAPER NUMBER**
1644	6

DATE MAILED: 11/21/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/480,236	Digan et al.
Examiner	**Group Art Unit**
Gerald Ewoldt	1644

☒ Responsive to communication(s) filed on *May 12, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-29* is/are pending in the application.

Of the above, claim(s) *19-28* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-18 and 29* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Restriction is required under 35 U.S.C. 121:

I. Claims 1-18 and 29, drawn to a recombinant immunotoxin polypeptide (RIP), classified in Class 424, subclass 183.1.

II. Claims 19 and 20, drawn to a nucleic acid encoding a RIP, classified in Class 514, subclass 44.

III. Claims 21-23 and 28, drawn to a method of treating a patient with a RIP *in vivo*, classified in Class 424, subclass 183.1.

IV. Claim 24, drawn to a method of treating a patient's cell population *in vitro* with a RIP, classified in Class 424, subclass 183.1.

V. Claims 25 and 26, drawn to a method of treating a donor cell population *in vitro* with a RIP, classified in Class 424, subclass 183.1.

VI. Claim 27, drawn to a method of treating a patient to be transplanted with a RIP, classified in Class 424, subclass 183.1.

The inventions are distinct, each from the other because:

2. Inventions I and II are different products. They are distinct because their structures and/or modes of action are different. The nucleic acid of Invention II is related to the polypeptide of Invention I by virtue of encoding same. However, nucleic acids and polypeptides are physically and functionally distinct chemical entities. Therefore, Invention I and II are patentably distinct.

3. Inventions I and III-VI are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)).

In the instant case, the product as claimed can be used in materially different processes, such as for antibody production.

4. Inventions III - VI are different methods. These inventions require different additional reagents acting through different process steps with different modes of operation and different endpoints. Therefore they are patentably distinct.

5. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

6. During a telephone conversation with Diane Furman on 11/13/00 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-18 and 29. Affirmation of this election must be made by applicant in replying to this Office action. Claims 19-28 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-18 and 29 are being acted upon.

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures. Specifically, the sequences in Figures 1 and 15 must be identified in the Description of the Figures by SEQ ID NO:.

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 4, 8, 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A RIP comprising a single chain Fv UCHT1-PE38 (UCHT-1:anti-CD3ε antibody; PE38:*Pseudomonas* exotoxin A 38 kD immunotoxin) fusion protein,

does not reasonably provide enablement for:

A) A RIP ... which binds an epitope formed by the ε and γ chains of human CD3,

B) A RIP ... comprising an antibody having a variable region which is at least 80% identical to the variable region of UCHT-1,

C) A RIP ... having residues 2-601 or 3-601 of SEQ ID NO:1 ... and polypeptides which are at least 80% identical thereto.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the breadth of the compositions encompassed by the claims.

Regarding A, the specification discloses a single functional construct, said construct comprising the UCHT-1 antibody. Said antibody is known to bind only the CD3ε chain (see Pharmingen Technical Data Sheet, 2000). The specification discloses two additional anti-CD3 antibodies: SP34, which the specification describes as being anti-CD3ε chain and BC-3, which is also anti-CD3ε chain (see Anasetti et al., 1992, page 845, column 2, paragraph 3). No antibodies or constructs capable of binding both the CD3 ε and γ chains are disclosed.

Regarding B and C, the specification provides no guidance as to which amino acids may be changed or deleted while antibody ligand-binding activity is retained. Just one anti-CD3 antibody is disclosed (UCHT-1) absent any substitutions or deletions. Given the open percent homology claim language, the total number of claimed antibodies is essentially unlimited because the number of potential substitutions is essentially unlimited. Given the lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain ligand-binding activity, and the fact that the relationship between the sequence of a protein and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require an undue amount of experimentation for one of skill in the art to select substitutions to the UCHT-1 antibody structure that retain ligand-binding activity.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the

lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 8, 17, and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

There is insufficient written description to show that Applicant was in possession of an antibody having a variable region which is at least 80% identical to the variable region of UCHT-1. No such variants of the UCHT-1 antibody are disclosed in the specification. Given the essentially unlimited number of antibodies encompassed by the claims, one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 13 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the laboratory designation "PE38" renders the claim ambiguous and indefinite.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-18 and 29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,103,235 (2000) in view of Thompson et al. (1995) and Kreitman et al. (1995) or U.S. Patent No. 5,489,525 (1996).

The '235 patent teaches a RIP comprising a single chain Fv (which is an F_{ab} fragment) UCHT-1 CD3ε binding domain and a diphtheria toxin (DT) (an ADP-ribosylating exotoxin) (see entire document, particularly column 19 lines, 21-30). The reference further discloses a RIP pharmaceutical composition comprising a single chain Fv fused to the carboxy terminus of the exotoxin in a V_L - L - V_H - C - exotoxin conformation (see particularly Figure 12).

The reference teachings differ from the claimed invention in that they do not teach the use of PE38 as the ADP-ribosylating exotoxin in the RIP construct.

Thompson et al. teaches that DT immunotoxins are problematic in human treatment protocols because of the potential anti-DT antibody titer already present in most people previously immunized to DT. The reference further teaches that one way to overcome this problem would be to use PE immunotoxins (see particularly page 28037, column 2, first paragraph).

Kreitman et al. and the '525 patent teach immunotoxic antibody - PE38 fusion proteins (see particularly, Figure 1 in Kreitman et al. and Figure 2A in the '525 patent).

From the teachings of the references it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a RIP, as taught by the '235 patent substituting the PE38 exotoxin for the DT exotoxin, as taught by Kreitman et al. or the '525 patent. One of ordinary skill in the art would have been motivated to make said substitution because PE exotoxin might be superior to a DT exotoxin given that most humans have pre-existing antibodies to DT (due to prior immunizations) which might interfere with its immunotoxic activity, as taught by Thompson et al.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday and alternate Fridays from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application

should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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November 15, 2000

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